PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : A61K 47/00

A1

(11) International Publication Number: WO 89/ 04673

(43) International Publication Date: 1 June 1989 (01.06.89)

(21) International Application Number: PCT/US88/04208

(22) International Filing Date: 23 November 1988 (23.11.88)

(31) Priority Application Number: 124,705

(32) Priority Date: 24 November 1987 (24.11.87)

(33) Priority Country: US

(60) Parent Application or Grant
(63) Related by Continuation
US 124,705 (CIP)
Filed on 24 November 1987 (24.11.87)

(71) Applicant *(for all designated States except US)*: BOARD OF REGENTS OF THE UNIVERSITY OF TEXAS SYSTEM[US/US]; 201 West Seventh Street, Austin, TX 78701 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : MCGINITY, James, William [US/US]; 4209 Dunning Lane, Austin, TX 78746 (US). CHANG, Kuei-Tu [TW/US]; 2501 Lake Austin Boulevard, Apartment B206, Austin, TX 78703 (US).

(74) Agent: FELLOWS, Charles, C.; FMC Corporation, 2000 Market Street, Philadelphia, PA 19103 (US).

(81) Designated States: AT (European patent), AU, BB, BE (European patent), BG, BJ (OAPI patent), BR, CF (OAPI patent), CG (OAPI patent), CH (European patent), CM (OAPI patent), DE (European patent), DK, FI, FR (European patent), GA (OAPI patent), GB (European patent), HU, IT (European patent), JP, KR, LK, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL (European patent), NO, RO, SD, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US.

Published
With international search report.

(54) Title: METHOD FOR PREPARING A SOLID SUSTAINED RELEASE FORM OF A FUNCTIONALLY ACTIVE COMPOSITION AND THE DOSAGE FORM SO OBTAINED

(57) Abstract

The invention is a sustained release dosage or delivery form, such as a tablet, pill, granule or the like capable of providing sustained release of a functionally active ingredient and the method for its manufacture. The invention comprises a matrix of a polymer containing functionally active ingredient and an excipient shaped into a form such as a granule, tablet or the like. Preferably the excipient is a microcrystalline cellulose.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	ML	Mali
AU	Australia	GA	Gabon	MR	Mauritania
BB	Barbados	GB	United Kingdom	MW	Malawi
BE	Belgium	HU	Hungary	NL	Netherlands
BG	Bulgaria	IT	Italy	NO	Norway
BJ	Benin	JP	Japan	RO	Romania
BR	Brazil	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic			SE	Sweden
CG	Congo	KR	Republic of Korea	SN	Senegal
CH	Switzerland	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
DE	Germany, Federal Republic of	LU	Luxembourg	TG	Togo
DK	Denmark	MC	Monaco	US	United States of America
FI	Finland	MG	Madagascar		

METHOD FOR PREPARING A SOLID SUSTAINED RELEASE FORM OF A FUNCTIONALLY ACTIVE COMPOSITION AND THE DOSAGE FORM SO OBTAINED

This invention relates to a method for preparing a dosage form, such as a tablet, a bead or the like, with a controlled and delayed release of the active ingredient and the controlled release dosage form made by the process.

It is known to produce solid pharmaceutical or other functionally active preparations which ensure a sustained release of an active ingredient over a long period of time and thus ensure a constant concentration of active ingredient in the body. These delayed release forms make it possible to reduce the number of doses of the drug to be administered daily and thus simplify the treatment plan considerably. Usually delayed release tablets and capsules are provided with a coating which regulates the release of active ingredient.

One disadvantage of relying on coatings for the delayed release property is that any inadvertent puncture of the coating or division of the tablet critically affects the coating integrity or the total surface area of the tablet, that is, some of the barrier coating effectiveness is lost. As a result, the characteristics of the release of active ingredient are significantly altered, so that in many cases, the delayed release tablets no longer have the property of delayed and continuous release of an active ingredient.

In addition, tablets with score lines are known which enable the tablets to be divided into partial doses in order to meet special therapeutic requirements. Divisible tablets of this kind must, in particular, satisfy the requirement of being easy and safe to divide and of ensuring precise dosage, even when broken into fragments.

Microencapsulated formulations do not wholly overcome the problem of controlled release because the film-forming agent frequently forms a continuous phase after a period of time making it impossible to maintain reproducible release rates. U.S. Patent No. 4,716,041 to Kjornaes et al. teaches a microencapsulated formulation of a first, inner film-forming coating, a second, outer film coating. The coated formulations are subsequently heated to permit the inner film-forming coating to form a continuous phase with uniform diffusion characteristics with time. Such a multiple coating process adds to the expense of a formulation and does not overcome the problem of coating integrity for tablets, caplets and other dosage forms.

Orally administerable pharmaceutical preparations are known in which the active substance is embedded in a polymer or matrix. The matrix slowly dissolves or erodes to release the pharmaceutically active ingredient. The feed formulations of pharmaceutical preparations of this kind are normally produced by dissolving the active ingredient together with a polymer in a solvent, then evaporating the solvent and granulating the solid mixture. Frequently the removal of the solvent and the granulation are carried out in a single operation by spray drying.

Pharmaceutical preparations of this type are intended for the purpose of distributing the active ingredient in a finely dispersed form through the polymer and increasing the surface area of the substance which is to be dissolved, so as to accelerate and not delay the dissolving process.

U.S. Patent 4,547,359 teaches that a divisible polyacrylate-based tablet may be formed of a compressed composition comprising a finely divided polyacrylate material having the active ingredient incorporated therein in molecular dispersion, and conven-

tional tablet excipients. However, the patent teaches it is particularly important to use a specific acrylate polymerized by emulsion polymerization and having a particle size of about 140 nm. Polyacrylates prepared by other methods, such as by solution or block polymerization, are unsuitable for purposes of the invention. In order to ensure a delayed release of the active ingredient, the active ingredient embedded in the polyacrylate material should have diffusion coefficients of 10^{-5} to 10^{-7} cm^2 per hour. However, it is undesirable to restrict the pharmaceutically active compounds to such a narrow range of diffusion coefficients.

U.S. Patent 4,692,337 to Ukigaya et al. teaches that prior art formulations based on a water-insoluble or slightly water soluble matrix have two disadvantages, the weight percentage of the matrix material must be 50% or more of the total weight, and that the rate of release of the medication rapidly decreases with time. Instead, the patent teaches dry mixing 100 parts of the active ingredient, theophylline, with 5 to 200 parts of ethyl cellulose and compressing the mixture into tablets.

Polylactic acid (PLA) is a well-known biologically compatible, insoluble polymeric body employed for the sustained release of pharmaceutical ingredients. U.S. Patent 4,357,312 teaches an implantable matrix suitable for dispensing pharmaceutical ingredients in which the pharmaceutical ingredient is dissolved in a mixture of polylactic acid, solvent and water. Freezing the water creates channels, and subsequent drying removes the solvent and water. The freezing conditions must be carefully controlled to make the release of the pharmaceutical ingredient uniform.

U.S. Patent 4,659,588 discloses bioerodable polymers useful to form coatings including polycarboxylic acids, polyamides, polylactic acid, polyglycolic acid

and the like.

U.S. Patent 4,666,702 teaches a drug delivery tablet containing a central core and a coating which is a thermoplastic polymer, optionally polylactic acid, nylon, polyglycolic acid and the like.

U.S. Patent 4,652,441 teaches a microcapsule or bead suitable for controlled release of a water soluble pharmaceutical ingredient including an oil layer thickened with polylactic acid.

The present invention overcomes the disadvantages of the prior art processes. The invention is a method for preparing a sustained release dosage or delivery form comprising blending a dosage amount of a functionally active ingredient, an excipient and a polymer having a glass transition temperature of about 30°C to about 150°C into a feed formulation, said polymer being present in sufficient quantity to form a matrix containing the functionally active ingredient, processing at least part of the feed formulation into a shaped form, and maintaining the shaped form at or above the glass transition temperature of the polymer for a sufficient time to provide a dosage form having controlled, sustained release of the functionally active ingredient when the dosage form is administered.

Polymers are known to be useful for forming a matrix-type sustained release dosage form. It has unexpectedly been found that a polymer having a glass transition temperature of about 30°C to about 150°C when maintained at or above the glass transition temperature in the presence of an excipient and a functionally active ingredient is capable of a controlled, sustained release of the ingredient even when the polymer comprises as little as 5% by weight. A polymer with a glass transition temperature of

about 40°C to about 100°C is preferred because of thermal stability and to provide a dosage form having controlled sustained release property which does not require refrigeration during shipment or storage in tropic climates.

Although the invention is disclosed in terms of a unitary matrix tablet, the scope of the invention is intended to include any matrix form such as a tablet, bead, microcapsule, densified nonpariel, pill, granule and the like comprised of a functionally active ingredient, an excipient and any polymer having a glass transition temperature from about 30°C to about 150°C. The shaped form may subsequently be reprocessed into other dosage forms. For example, granules or small pills may be processed into capsules, or may be tabletted.

Exemplary polymers include low (branched) and high (linear) density polyethylene, polypropylene, poly(propylene/ethylene), polyisobutylene and higher homologs, poly(ethylene/isobutylene), poly(isoprene/-isobutylene), ethylene/propylene/diene terpolymers (EPDM), methyl methacrylate polymers or copolymers from acrylic, methacrylic, hydroxyalkyl acrylic or methacrylic, acrylic or methacrylic acids or their methyl, ethyl or lauryl esters, polyacrylonitrile, vinyl acetate homopolymer or copolymers with vinyl stearate, 2-ethylhexyl acrylate or ethyl acrylate, poly (vinyl butyral), poly(vegetable oil acid/-ethylene diamine), polyoxymethylene, poly(ethylene oxide), cellulose acetate, acetate butyrate, propionate, acetate propionate, ethylcellulose, poly-(ethylene terephthalate) or other polyesters of polyhydric alcohols and dicarboxylic acids, polyether, polyester or polyester/polyamide polyurethanes, poly dimethyl-siloxane or other polysilicones, allyl diglycol carbonate prepolymers and furane resins. Additional polymers include methylcellulose, hydroxy-

propyl cellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, polyvinyl alcohol, polyvinyl acetate, hydroxypropylmethyl cellulose phthalate, polyhydroxy butyrate, polyhydroxy valerate, polycaprolactone, polylactic acid, polyglycolic acid, polylactic co-glycolic acid, polyglutamic acid, polyanhydrides, polyethylene glycols and polypropylene glycols.

It is desirable for the polymers to be either biodegradable or bioerodable, and if to be used to control the release of pharmaceutically active compounds to be pharmaceutically acceptable.

Particularly desirable polymers are polyisobutylene, polymers or copolymers of acrylic acid, methacrylic acid, hydroxyalkylacrylic acid, hydroxyalkylmethacrylic acid or their methyl, ethyl or lauryl esters. Other particularly desirable polymers include poly(ethylene oxide), cellulose acetate, cellulose acetate butyrate, cellulose acetate proprionate, ethyl cellulose, polyesters of polyhydric alcohols and dicarboxylic acids, polyethers, cellulose acetate phthalate, dl-polylactic acid, polyglycolic acid, polylactic-polyglycolic copolymers, polycaprolactone, polyhydroxybutyrate, polyhydroxyvalerate and polyethylene glycols.

Any functionally active ingredient may be employed in the present invention, such as a pharmaceutically active ingredient, a flavor, a fragrance, an insecticide, a herbicide, a veterinary product or the like. Particularly desirable are pharmaceutically active ingredients, preferably pharmaceutically active ingredients selected from the group consisting of theophylline, quinidine sulfate, propanolol, chloropheniramine, testosterone and ethenyl estradiol.

Preferred commercial polymers are marketed under

the name polyglycolic acid, poly(d,l)lactic acid and poly(d,l)lactic co-glycolic acid (85:15 and 50:50 copolymers) by DuPont and are described in product bulletins "Glycolide S.G." May, 1988 and "Medisorb Bioresorbable Polymers" August, 1988 and both are incorporated herein by reference. The polymers are respectively also called poly(glycolide), poly(d,l-lactide) and poly(D,L-lactide-co-glocolide) in Boehringer Ingelheim's product bulletin "Resorbable Polyesters" which is also incorporated herein by reference. The polymers may be obtained in a range of molecular weights and inherent viscosities.

The polymer, such as dl-polylactic acid (PLA), can be introduced into the feed formulation by any convenient method such as dry mixing, wet granulation method or with a solvent system. In the latter method, the polymer is dissolved in methylene chloride and then blended into the functionally active ingredient and excipient. A lubricant or other additive such as a colorant may be optionally added. The intended scope of the invention includes any polymer having a glass transition temperature above about 30°C. However, polymers having a glass transition temperature of over 150°C may result in decomposition of the functionally active ingredient or of the excipient. A glass transition temperature of less than 100°C is preferable for use with many thermally unstable ingredients, such as hydrates.

Heating a dosage form of a pharmaceutically active compound is contrary to the basic practice of pharmacology. One skilled in the art of pharmacology avoids exposure of a dosage form to heat unless absolutely necessary and unless explicitly required, and even then is cooled to minimize the heat to which the active compound is exposed.

Alternatively, the blend can be wet granulated with an aqueous latex dispersion of the polymer which

is used as the binding solution. The air dried granulation is then blended with the lubricant and processed into a shaped form.

Drug release is quite rapid for tabletted formulations made by either of these procedures with polylactic acid as the polymer. In less than thirty minutes the drug is fully released into the dissolution medium. As the level of polymer is increased in the formulation from zero percent, no significant retardation of release is achieved.

When no polymer is present in the tablet the tablet hardness decreases as the time of heating increases. On the other hand, the hardness increases with tablets containing polymer as the time of heating increases. The hardness continuously increases with tablets containing at least 15% polymer. With tablets containing 5% to 10% polymer the hardness increases to a plateau. For the purpose of this invention all percentages are expressed as weight percent. Any quantity of polymer may be employed which is sufficient to form a matrix containing the functionally active ingredient, desirably 1% to 90% polymer is sufficient, preferably 5% to 50% polymer. As used herein the term "maintaining the shaped form at or above the glass transition temperature" is intended to include heating by any conventional means prior to administering but does not include thermal effects from compression alone.

Any convenient excipient may be employed in the feed formulation. The excipient may be employed for a single function such as a diluent, a binder, a lubricant, a disintegrant, an adsorbent, or for a combination of functions. Common excipients such as lactose, dicalcium phosphate, calcium sulfate, sugars, microcrystalline cellulose, gums, methylcellulose, starch, polyvinylpyrrolidone, clay and the like may be selected by one skilled in the art to

provide their usual contribution to the dosage form. The excipient may be employed in an amount varying from 1% to about 90% by weight.

Particularly desirable excipients are marketed under the tradename of Avicel brand microcrystalline cellulose by FMC Corporation. Microcrystalline cellulose is suitable for use as a binder, a diluent and as a disintegrant. The Avicel PH grades of microcrystalline cellulose are preferred for use in compression shaping. The product is porous which permits the microcrystalline cellulose to absorb a liquid ingredient while remaining a free-flowing powder suitable to serve as a feed formulation for compression. Microcrystalline cellulose also provides an intermediate disintegration rate between the rapid disintegration rate of soluble excipients and the very slow disintegration rate of insoluble excipients such as calcium sulfate.

A polymer, such as polylactic acid, is brittle below its glass transition temperature. The glass transition temperature ("Tg") or second order transition temperature is the temperature at which a polymer changes from a brittle material (glassy state) to a rubbery material. The glass transition temperatures of polymers vary with molecular weight. The glass transition, unlike a true thermodynamic transition, takes place over a temperature range of several degrees and is dependent upon the experimental method and the time scale used for its determination. The glass transition temperature can also vary with the additives employed such as plasticizers, lubricants and the like. Below the transition, the majority of the polymer chains have a fixed configuration and little translation or rotation of chains takes place. Methods used to determine the glass transition temperature and the reported values for a large number of polymers are available in standard refer-

ences employed by those skilled in the art. For the purpose of this invention the glass transition temperature shall include a temperature below the melting point of a polymer at which the polymer ceases to be a brittle, glassy or crystalline solid and becomes rubbery or begins to flow.

Shaped forms of PLA, a functionally active ingredient and an excipient which have been processed into shaped forms and heated but not heated to the glass transition temperature are usually erratic in their rate of dissolution. Further, the hardness of the shaped forms decreases on heating below the glass transition temperature. However, when heated to or above their glass transition temperature the shaped forms form a matrix. They become consistent in their rate of dissolution and their hardness increases. Further, the rate of dissolution decreases with an increase of concentration of PLA and with the length of time the shaped forms are held at or above the glass transition temperature.

The following examples will explain to one skilled in the art the best mode of practicing the invention.

EXAMPLE 1

FEED FORMULATION PROCEDURES

Feed formulations were prepared containing 0%, 5%, 10% and 15% PLA. The functionally active ingredient employed was theophylline and the excipient employed was Avicel PH 101 brand microcrystalline cellulose. 0.5% magnesium stearate was added as a lubricant. Dosage units of 300 mg containing 75 mg theophylline were compressed in a tablet press from a feed formulation containing as follows: 25% theophylline, 74.5% excipient and 0.5% lubricant (0% PLA); 25% theophylline, 69.5% excipient, 0.5% lubricant and 5% PLA; 25% theophylline, 64.5% excipient,

0.5% lubricant and 10% PLA; and 25% theophylline, 59.5% excipient, 0.5% lubricant and 15% PLA.

Although the invention is exemplified in terms of theophylline as the functionally active ingredient, microcrystalline cellulose as the excipient and magnesium stearate as the lubricant, it will be clear to one skilled in the art that any suitable functionally active ingredient, excipient or lubricant may be employed. A dosage amount of a functionally active ingredient can vary over a wide range depending on activity and time of sustained release. Generally 5% to about 50% of the functionally active ingredient will be contained in the matrix.

The feed formulations were prepared by two methods, dissolving the PLA in methylene chloride and adding the solution to the blend of the pharmaceutical ingredient and excipient (the "Organic" method), or by incorporating the PLA as an aqueous latex dispersion (the "Latex" method). The aqueous latices were prepared by emulsion of the organic solution of the polymer with a Gaulin brand laboratory homogenizer. Subsequently, the organic solvent was removed by evaporation. After air drying of the granules a lubricant was added to the feed formulation and 300 mg tablets were formed by direct compression to about 5.5 kg. to 6 kg. The PLA had a glass transition temperature of 55°C to 57°C.

The hardness, friability and dissolution rates (U.S.P. Method II) of tablets were determined. The hardness and friability results are presented as Tables IA and IB. The dissolution data are presented as Runs 2A to 6C. The numbers to the right of the decimal point indicate a different level of the variable under study in that series with 0 indicating a control.

Run 1A: The percentage change of hardness on heating up to 24 hours at 60°C is presented as Table

IA for tablets prepared by the Organic method.

Run 1B: The friability of tablets prepared by the Organic method is presented as Table IB as a function of PLA content and time of heating.

Dissolution Runs - Table II.

Run 2A: The rate of dissolution of theophylline is compared for 15% PLA tablets prepared by the solvent method heated for up to 12 hours at 40°C, less than the glass transition temperature.

Run 2B: The rate of dissolution of theophylline is compared for 15% PLA tablets prepared by the solvent method heated for up to 12 hours at 60°C, slightly above the glass transition temperature.

Run 2C: The rate of dissolution of theophylline is compared for 15% PLA tablets prepared by the solvent method heated for up to 24 hours at 60°C, slightly above the glass transition temperature.

Run 3A: The rate of dissolution of theophylline is compared for 5% PLA tablets prepared by the solvent method and heated at 60°C for up to 24 hours.

Run 3B: The rate of dissolution of theophylline is compared for 5% PLA tablets prepared by the solvent method and heated at 60°C for up to 12 hours.

Run 4: The rate of dissolution of theophylline from 10% PLA tablets prepared by the Organic method and by the Aqueous Latex method are compared after heating at 60°C for 1 and 12 hours.

Run 5A: Rates of dissolution of theophylline are compared for tablets (Aqueous Latex method) containing 5%, 10% and 15% PLA and heated for 1 hour at 60°C.

Run 5B: Rates of dissolution of theophylline are compared for tablets (Aqueous Latex method) containing 5%, 10% and 15% PLA and heated 6 hours at 60°C.

Run 6A, 6B and 6C: Rates of dissolution of theophylline are compared for tablets containing 5%, 10%

and 15% PLA after heating to 60°C for up to 24 hours.

From the above data it is clear that the rate of dissolution of a pharmaceutically active ingredient can be controlled by the quantity of polylactic acid or other polymer incorporated into the feed formulation, the method of incorporation, and the time the tablets are maintained at or above the glass transition temperature.

EXAMPLE 2

The influence of thermal treatment was determined on the dissolution properties of drugs from tablets containing various biodegradable polymers. Unless specified otherwise, tablets were prepared from formulation typically containing 25% of a functionally active ingredient, 60% Avicel PH 101 microcrystalline cellulose and 15% polymer. No lubricant was employed.

The functionally active ingredient was mixed with the microcrystalline cellulose for 5 minutes. Granules were prepared by dissolving the polymer in methylene chloride to distribute the polymer homogeneously throughout the matrix. The granules were air dried at 25°C overnight and tablets were compressed to a weight of 500 mg with a Carver laboratory press at 750 kg pressure. Heat treated tablets were heated at 60°C for 24 hours. Polymers employed were:

Poly-(dl-Lactide) High MW (UT), Tg 35°C-40°C, [PLA-HMV]; Poly-(dl-Lactide) Low MW, Tg 40°C-45°C, [PLA-LMW]; Poly-(l-Lactide), Tg 55°C-60°C, [L-PLA]; Polycaprolactone 300, mp 60°C-62°C, [PCL-300]; Polycaprolactone 700, mp 60°C-62°C, [PCL-700]. The abbreviations to be used herein for the polymers appear in square brackets.

Functionally active ingredients employed were:

Theophylline,

Chlorpheniramine Maleate,

Propanolol Hydrochloride, and
Quinidine Sulfate.

Rate of dissolution of matrix tablets with and without heat treatment were compared according to the method of Example 1. Results are presented as Table III.

Runs 1 and 7 show the rate of dissolution is not a function of the polymer alone, but that the excipient and/or functionally active ingredient also is a factor in controlling the rate of dissolution.

Run 8 is surprising in that the optically active polymer appears ineffective with the same formulation of ingredients that is effective with the racemic polymer. This run indicates that the effect of thermal treatment is unexpected.

EXAMPLE 3

Tablets were prepared as before containing 25% theophylline, 60% Avicel PH 101 brand microcrystalline cellulose and 15% polymer. The polymers were, Run 1, DuPont Medisorb 5050 brand of a 50:50 Poly-(D,L)lactic co-glycolic acid polymer, [PLA:PGA], Tg 60°C-65°C; Run 2, polyethylene glycol mw 20,000, [PEG 20M]; and Run 3, Ritt Chemical polyisobutylene, [PIB], pour point 112.5°C. The percent theophylline released with time (hours) was: Run 1, no heat treatment; 10%, 0.7 hour; 17%, 1.3 hours; 25%, 2 hours; 39%, 4 hours; 49%, 6 hours and 71%, 12 hours. Run 1, heated 24 hours at 67°C; 10%, 0.7 hour; 18%, 1.3 hours; 32%, 2 hours; 39%, 4 hours; 47%, 6 hours; and 60%, 12 hours.

Run 2, no heat treatment; 10%, .5 hour; 17%, 1 hour, 29%, 2 hours; 88%, 4 hours; and 100%, 6 hours. Run 2, heated 59°C, 24 hours; 10%, .5 hour; 19%, 1 hour, 39%, 2 hours; 73%, 4 hours; and 94%, 6 hours. Here the PEG tablets heat treated 24 hours at 59°C are outstanding in that their rate of release of theophylline is a straight line function of time.

Run 3, no heat treatment 50%, 0.5 hour; 77%, 1 hour; 98%, 2 hours; and 100%, 4 hours.

Run 3, heated 60°C, 24 hours; 79%, 0.5 hour, 92%, 1 hour; 96%, 2 hours; and 97%, 4 hours. Here the rate of release is initially greater with heat treatment but slows sufficiently so that the functionally active ingredient is still being released after the non-heat treated tablet is exhausted.

TABLE IA

INFLUENCE OF 60°C HEAT ON HARDNESS
PLA TABLET

Hours at 60°C	% of Initial Hardness			
	0% PLA	5% PLA	10% PLA	15% PLA
0	100	100	100	100
1	93	104	100	103
3	94	104	NA	107
6	90	103	107	NA
12	85	104	107	108
24	87	104	105	110

TABLE IB

INFLUENCE OF 60°C HEAT ON FRIABILITY
PLA TABLET

Hours at 60°C	% Loss of Friability			
	0% PLA	5% PLA	10% PLA	15% PLA
1	0.10	0.09	0.05	0.04
3	0.13	0.08	NA	0.03
6	0.12	NA	0.05	0.04
12	0.13	0.06	0.04	0.03
24	0.12	0.06	0.04	0.02

TABLE II

RELEASE RATE OF TABLETS CONTAINING 25% THEOPHYLLINE

Run	% PLA Polymer	Heat Treated	Percent Dissolved In							
			% 0.5 hr.	% 1 hr.	% 2 hr.	% 3 hr.	% 6 hr.	% 12 hr.	% 24 hr.	% 48 hr.
2A.0	15%	None	98	100	100	100	100	100	-	-
2A.1	15%	1 hr. 40°C	28	39	52	-	65	80	-	-
2A.2	15%	6 hr. 40°C	25	32	42	-	62	80	-	-
2A.3	15%	24 hr. 40°C	24	30	40	-	61	78	-	-
2B.0	15%	None	98	100	100	100	100	100	-	-
2B.1	15%	1 hr. 60°C	22	31	40	50	63	80	-	-
2B.2	15%	6 hr. 60°C	18	26	35	NA	51	66	-	-
2B.3	15%	24 hr. 60°C	16	23	33	NA	50	64	-	-
2C.0	15%	None	98	100	100	100	100	-	-	-
2C.1	15%	1 hr. 60°C	22	30	40	45	64	82	95	-
2C.2	15%	6 hr. 60°C	18	26	35	-	52	64	88	-
2C.3	15%	24 hr. 60°C	16	23	33	-	50	63	79	-

TABLE II (cont'd.)

Run	% PLA Polymer	Heat Treated	Percent Dissolved In							
			% 0.5 hr.	% 1 hr.	% 2 hr.	% 3 hr.	% 6 hr.	% 12 hr.	% 24 hr.	% 48 hr.
3A.0	5%	None	NA	98	100	100	100	100	-	-
3A.1	5%	1 hr. 60°C	-	27	45	59	81	86	99	-
3A.2	5%	12 hr. 60°C	-	26	44	58	80	85	98	-
3A.3	5%	24 hr. 60°C	-	26	43	58	80	84	99	-
3B.0	5%	None	98	100	100	100	100	100	-	-
3B.1	5%	1 hr. 60°C	33	50	59	79	82	93	-	-
3B.2	5%	12 hr. 60°C	32	44	58	79	80	93	-	-
3B.3	5%	24 hr. 60°C	31	-	-	78	80	88	-	-
4L.1	10%	1 hr. 60°C	21	-	74	-	-	92	-	-
4L.2	10%	12 hr. 60°C	20	25	58	-	-	91	-	-
40.1	10%	1 hr. 60°C	20	25	45	-	-	80	-	-
40.2	10%	12 hr. 60°C	19	24	-	-	-	68	-	-

TABLE II (cont'd.)

Run	% PLA Polymer	Heat Treated	Percent Dissolved In							
			% 0.5 hr.	% 1 hr.	% 2 hr.	% 3 hr.	% 6 hr.	% 12 hr.	% 24 hr.	% 48 hr.
5A.1	5%	1 hr. 60°C	-	58	85	86	-	100	100	100
5A.2	10%	1 hr. 60°C	-	22	43	67	-	75	100	100
5A.3	15%	1 hr. 60°C	-	0	18	20	-	26	68	76
5B.1	5%	6 hr. 60°C	24	-	46*	80	-	85	84	-
5B.2	10%	6 hr. 60°C	20	-	38*	55	-	85	85	-
5B.3	15%	6 hr. 60°C	9	-	21*	25	-	61	78	-
6A.1	5%	1 hr. 60°C	58	-	90*	91	-	100	-	-
6A.2	5%	6 hr. 60°C	24	-	52*	80	-	92	-	-
6A.3	5%	12 hr. 60°C	23	-	40*	63	-	92	-	-
6A.4	5%	24 hr. 60°C	22	-	40*	53	-	88	-	-

TABLE II (cont'd.)

Run	% PLA Polymer	Heat Treated	Percent Dissolved In							
			% 0.5 hr.	% 1 hr.	% 2 hr.	% 3 hr.	% 6 hr.	% 12 hr.	% 24 hr.	% 48 hr.
6B.1	10%	1 hr. 60°C	-	21	46*	73	-	93	-	-
6B.2	10%	6 hr. 60°C	-	18	37*	52	-	91	-	-
6B.3	10%	24 hr. 60°C	-	16	31*	43	-	81	-	-
6C.1	15%	1 hr. 60°C	10	-	-	32	-	69	82	98
6C.2	15%	6 hr. 60°C	10	-	-	32	-	68	82	98
6C.3	15%	12 hr. 60°C	10	-	-	32	-	68	82	97
6C.4	15%	24 hr. 60°C	10	-	-	32	-	63	82	98

* 1 1/2 hour

TABLE III

EFFECT OF HEAT TREATMENT ON RATE OF DISSOLUTION
OF FUNCTIONALLY ACTIVE INGREDIENTS (FIA) FROM POLYMERS

Run	Polymer	FAI	Heat Treated	Percent Dissolved In					
				% 0.5 hr.	% 1 hr.	% 2 hr.	% 4 hr.	% 6 hr.	% 14 hr.
1	PLA(LMW)	Theophylline	N	85	98	103	104	-	-
			Y	52	85	100	105	-	-
2	PLA(300)	Theophylline	N	42	60	81	96	102	104
			Y	20	32	47	63	73	92
3	PCL(700)	Theophylline	N	15	21	32	43	53	73
			Y	8	13	19	27	33	44
4	PLA(HMW)	Chlorphenir-amine	N	25	42	66	91	100	105
			Y	19	28	47	68	88	104
5	PLA(HMW)	Quinidine Sulfate	N	15	25	37	54	66	87
			Y	11	16	25	36	48	64

TABLE III (cont'd.)

Run	Polymer	FAI	Heat Treated	Percent Dissolved In					
				% 0.5 hr.	% 1 hr.	% 2 hr.	% 4 hr.	% 6 hr.	% 14 hr.
6	PLA(HMW)	Propanolol	N	43	59	79	98	101	
			Y	26	39	58	77	90	
7	PLA(LMW)	60% Theo-phylline*	N	42	66	93	100	102	103
			Y	21	42	74	97	101	103
8	LPLA	Theophylline	N	86	99	100	100		
			Y	86	98	100	100		

*60% Theophylline, 25% excipient, 15% polymer

Claims:

1. A method for preparing a sustained release dosage form comprising blending into a feed formulation a dosage amount of a functionally active ingredient, an excipient and polymer having a glass transition temperature of 30°C to 150°C, said polymer being present in sufficient quantity to form a matrix containing the functionally active ingredient, processing at least part of the feed formulation into a shaped form characterized by maintaining the shaped form at or above the glass transition temperature of the polymer for a sufficient time to provide a dosage form having controlled, sustained release of the functionally active ingredient when the dosage form is administered.

2. The method of claim 1 characterized in that the polymer in the feed formulation is selected from polyisobutylene, polymers or copolymers of acrylic acid, methacrylic acid, hydroxyalkylacrylic acid, hydroxyalkylmethacrylic acid or their methyl, ethyl or lauryl esters, poly(ethylene oxide), cellulose acetate, cellulose acetate butyrate, cellulose acetate proprionate, ethyl cellulose, polyesters of polyhydric alcohols and dicarboxylic acids, polyethers, cellulose acetate phthalate, dl-polylactic acid, polyglycolic acid, polylactic-polyglycolic copolymers, polycaprolactone, polyhydroxybutyrate, polyhydroxyvalerate and polyethylene glycols, mixtures and copolymers thereof to provide from 1% to 90% polymer in the dosage form.

3. The method of claims 1 or 2 characterized in that the polymer in the feed formulation is present in an amount to provide from 5% to 50% polymer, 1% to 90% excipient, and from 5% to 90% of the functionally active ingredient in the dosage form.

4. The method of claim 3 characterized in that

the shaped form is maintained at or above the glass transition temperature for from 1 to 12 hours.

5. An improved, sustained release dosage form comprising a shaped form containing a well mixed blend of a dosage amount of a functionally active ingredient, an excipient and a sufficient quantity of a polymer to form a matrix containing the functionally active ingredient, said polymer having a glass transition temperature of 30°C to 150°C, characterized by the shaped form having been heated at or above the glass transition temperature of the polymer for a sufficient time to provide a dosage form providing controlled release of the functionally active ingredient when the shaped form is administered.

6. The sustained release dosage form of claim 5 characterized by from 1% to 90% excipient, 5% to 90% functionally active ingredient and from 5% to 50% polymer selected from polyisobutylene, polymers or copolymers of acrylic acid, methacrylic acid, hydroxyalkylacrylic acid, hydroxyalkylmethacrylic acid or their methyl, ethyl or lauryl esters, poly(ethylene oxide), cellulose acetate, cellulose acetate butyrate, cellulose acetate proprionate, ethyl cellulose, polyesters of polyhydric alcohols and dicarboxylic acids, polyethers, cellulose acetate phthalate, dl-polylactic acid, polyglycolic acid, polylactic-polyglycolic copolymers, polycaprolactone, polyhydroxybutyrate, polyhydroxyvalerate and polyethylene glycol, mixtures and copolymers thereof.

7. The sustained release dosage form of claim 5 characterized in that the polymer has a glass transition temperature of 40°C to 100°C.

8. The sustained release dosage form of claims 5, 6 or 7 characterized in that the excipient is selected from microcrystalline cellulose, lactose, dicalcium phosphate, calcium sulfate, sugar,

microcrystalline cellulose, gums, methylcellulose, starch, polyvinylpyrrolidone and clay.

9. The sustained release dosage form of claim 8 characterized in that the form is a tablet, bead, microcapsule, pill or a granule.

10. The sustained release dosage form of claim 8 characterized in that the pharmaceutically active ingredient is selected from theophylline, quinidine sulfate, propranolol, chlorpheniramine, testosterone and ethenyl estradiol.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 88/04208

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC4: A 61 K 47/00

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC4	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	US, RE, 27107 (C. L. LEVESQE) 30 March 1971, see column 5, line 51 - line 57; column 6, line 37 - line 46; claims 1,6 --	1-9
X	UA, A, 4226848 (T. NAGAI ET AL.) 7 October 1980, see claim 1 --	1-3,5-6, 8-9
X	US, A, 4250163 (T. NAGAI ET AL.) 10 February 1981, see claim 1 --	1-3,5-6, 8-9
X	US, A, 4059686 (W. TANAKA ET AL.) 22 November 1977, see claims 1,3 --	1-3,5-6, 8-9

* Special categories of cited documents: [14]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
28th February 1989	17 MAR 1989
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	D.C. VAN DER PUTTEN

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category*	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	US, A, 4308251 (J. M. DUNN ET AL.) 29 December 1981, see claim 1 --	1-3,5-6, 8-9
X	US, A, 4499066 (L. MORO ET AL.) 12 February 1985, see claims 1-3 --	1-3,5-6, 8-9
X	US, A, 4647599 (D. BEZZEGH ET AL.) 3 March 1987, see claims 1,4 --	1-3,5-6, 8-9
X	GB, A, 2031917 (VEB JENAPHARM) 30 April 1980, see claims 1,2,4,10,11 --	1-3,5-6, 8-9
X	EP, A2, 0240904 (BASF AKTIENGESELLSCHAFT) 14 October 1987, see claims 1,4,5 --	1-3,5-6, 8-9
X	EP, A1, 0241178 (ROHTO PHARMACEUTICAL CO.) 14 October 1987, see claims 1,3,4 --	1-3,5-6, 8-9
X	Patent Abstracts of Japan, Vol 4, No 182, C 35, abstract of JP 55-122726, publ 1980-09-20 (ASAHI KASEI KOGYO K.K.) --	1-3,5-6, 8-9

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/US 88/04208

SA 25740

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 12/01/89
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-RE- 27107	30/03/71	NONE	
UA-A- 4226848	07/10/80	NONE	
US-A- 4250163	10/02/81	JP-A- 55118413	11/09/80
		US-A- 4226848	07/10/80
		DE-A-B,C 2908847	11/09/80
		GB-A-B- 2042888	01/10/80
		FR-A-B- 2450610	03/10/80
		CH-A- 638987	31/10/83
US-A- 4059686	22/11/77	FR-A-B- 2285896	23/04/76
		DE-A-C- 2542158	01/04/76
		JP-A- 51038412	31/03/76
		GB-A- 1516359	05/07/78
US-A- 4308251	29/12/81	GB-A-B- 2067072	22/07/81
		BE-A- 886998	08/07/81
		NL-A- 8100037	03/08/81
		FR-A-B- 2473308	17/07/81
		JP-A- 56103110	18/08/81
		DE-A-C- 3100191	10/12/81
		AU-D- 65976/81	16/07/81
		LU-A- 83052	10/09/82
		CA-A- 1140466	01/02/83
		SE-A- 8100104	12/07/81
		AT-A- 374681	25/05/84
		CH-A- 646604	14/12/84
		AU-A- 542824	14/03/85
		SE-A-C- 447450	17/11/86
US-A- 4499066	12/02/85	FR-A-B- 2510888	11/02/83
		DE-A-C- 3228999	24/02/83
		AU-D- 86606/82	10/02/83
		JP-A- 58029717	22/02/83
		BE-A- 894028	04/02/83
		NL-A- 8203057	01/03/83
		GB-A-B- 2107214	27/04/83
		SE-A- 8204581	04/08/82
		CH-A- 657046	15/08/86
		CA-A- 1217721	07/02/87
		SE-A-C- 454325	25/04/88
US-A- 4647599	03/03/87	SE-A- 8405615	12/05/85
		FR-A-B- 2554717	17/05/85

EPO FORM P0479

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/US 88/04208

SA 25740

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 12/01/89
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4647599	03/03/87	BE-A- 901007	08/05/85
		GB-A- 2149413	12/06/85
		DE-A- 3441308	23/05/85
		NL-A- 8403447	03/06/85
		CH-A- 665124	29/04/88
		SE-B- 455571	25/07/88
GB-A- 2031917	30/04/80	NL-A- 7906199	27/03/80
		FR-A- 2436606	18/04/80
		DE-A- 2930321	10/04/80
		JP-A- 55055121	22/04/80
		SE-A- 7907900	26/03/80
		JP-A- 55066521	20/05/80
		US-A- 4315909	16/02/82
EP-A- 0240904	14/10/87	AU-D- 71413/87	15/10/87
		DE-A- 3612212	15/10/87
		JP-A- 62242630	23/10/87
EP-A- 0241178	14/10/87	AU-D- 70616/87	01/10/87
		JP-A- 62223112	01/10/87